REMARKS

The Amendments to the Claims

Applicants have amended claim 4 to recite "full length" SEQ ID NO:5 in and high stringency conditions in paragraph (ii). Support for the amendments is found on, *e.g.*, in paragraphs [0014], [0015], [0039] and [0044].

In sum, upon entry of this amendment, claims 4, 5, 12, and 43-44 will be pending. None of the above amendments constitutes new matter; their entry is respectfully requested.

Applicants express their gratitude to the Examiner for the courtesy shown during the telephonic interview of October 20, 2006 with Walter Egbert, Attorney for Applicants and Kimberley Gavin, Agent for Applicants. During the interview, the enablement, written description and anticipation rejections were discussed. The Examiner has graciously allowed Applicants to submit this Supplemental Response, which addresses the issued discussed during the interview. Remarks made in the October 2, 2006 Response but not reiterated here are to be considered as responsive to the March 31, 2006 Office Action and considered by the Examiner, in addition to the new remarks made herein.

THE REJECTIONS

The Rejections Under 35 U.S.C. § 112 First Paragraph

The Claims Are Enabled And Meet The Written Description Requirement

The Office Action has rejected claims 1-2, 4-5, 7-8 and 11-12 under 35 U.S.C. § 101 and 35 U.S.C. § 112, 1st paragraph. To briefly summarize, the Office Action contends that the claimed invention is not supported by either a specific and/or substantial asserted utility or a well-established utility, and because of that, one skilled in the art would not know how to make and use the claimed invention. Applicants Response filed October 2, 2006 provided arguments and evidence, not reiterated here, that supports a biological role for the claimed polypeptide and its significance. In the Examiner's interview, the Examiner indicated that the rejections under 35 U.S.C. § 101 would be withdrawn. However, the Examiner indicated that the claimed invention still failed to meet the written description and enablement requirements.

The Office Action asserts, that there is insufficient guidance and direction as to how to make the claimed polypeptide or a derivative or homolog thereof, encoded by any nucleic acid sequence having at least about 65% similarity to SEQ ID NO:1 or 5 or capable of hybridizing to SEQ ID NO:1 or 5 under low stringency conditions. Without detailed description, the Office Action contends, a person of ordinary skill in the art would not be able to determine, without undue experimentation, which nucleic sequences encompassed by the instant claims would share the ability as a molecular marker of degenerative disease, other than SEQ ID NO:5 encoding SEQ ID NO:6.

For the same reasons articulated above with respect to the written description requirement, the Office Action contends that the claims are not enabled. Applicants respectfully traverse these rejections and respond to them both herein.

As amended herein, Applicants respectfully submit that the pending claims meet both the written description and enablement requirements. Applicants submit that it is well within the skill of one in the art to identify a nucleic acid or polypeptide sequence having the similarity as claimed in the instant claims. For instance, the specification teaches that the EST database at the National Center for Biotechnology Information (NCBI) was searched using the N8 VA-domain protein sequence as a query to identify EST sequences that contain the VA-domain. *See*, paragraph [0010]. The specification teaches that a series of overlapping EST clones with homology to N8 represented a novel VA protein, therein entitled WARP. *See*, paragraphs [0131] and [0153].

With respect to the contention that Applicants have not enabled or provided written description for "a derivative or homolog thereof," Applicants respectfully submit that the terms are enabled and supported by the specification, for at least the reasons set forth in the October 2, 2006 Response. To reiterate briefly, Applicants disclose "[a] homolog of murine origin comprises a VA-related domain having the amino acid sequence set forth in SEQ ID NO:8." Further, a "homolog" is defined as "an analogous polypeptide having at least about 65% similar amino acid sequence from another animal species or from a different locus within the same species." *See*, paragraph [0050]. Moreover, a search of the human genome database with the mouse WARP protein sequence identified a human protein with a predicted sequence with very high homology to the mouse WARP; that these proteins are homologs is clear "because

they share 79% amino acid identity (*see* Figure 1C). In addition, if conserved changes are considered in the analysis, they share 95% identity." See, paragraph [0142].

With respect to the contention that one ordinarily skilled in the art would not know how to use a polypeptide or nucleic acid of the instant invention as a molecular marker for ECM integrity, Applicants respectfully traverse. Applicants submit that the claims are not directed to the use of a polypeptide of the invention as a marker for ECM integrity. Rather, the claims are directed to an isolated polypeptide which "*in situ* forms part of the ECM in an animal." Applicants have ample support for the polypeptide as part of the ECM, as shown by the expression of WARP in cartilage (see, paragraphs [0050 and 0051], as well as by the teaching of Allen (discussed in the October 2, 2006 Response). On this basis, Applicants submit that the claims are enabled under 35 U.S.C. §112, ¶1.

Since the claims do not recite the use of a polypeptide of the invention as a marker for ECM integrity, Applicants submit that a showing of the correlation of WARP with ECM integrity is not necessary.

Nonetheless, Applicants submit that, given the teachings of the specification and as evidenced by Allen, one of skill in the art would know that WARP is normally associated with the ECM generally and interacts with perlecan. Moreover, one ordinarily skilled would know that perturbations in WARP function or level would have an effect on the ECM. In support of that argument, we note that, as discussed above, WARP interacts with perlecan, a protein component of the ECM and known to play an important role in cartilage formation. Applicants bring to the attention of the Examiner two publications published prior to the filing date of the instant application: Arikawa-Hirasawa *et al.*, "Perlecan is essential for cartilage and cephalic development," *Nat Genet.* 1999 Nov;23(3):354-8 ("Arikawa-Hirasawa I") and Arikawa-Hirasawa *et al.*, "Dyssegmental dysplasia, Silverman-Handmaker type, is caused by functional null mutations of the perlecan gene. *Nat. Genet.* 2001 Apr;27(4):431-4 ("Arikawa-Hirasawa II"), attached herewith at Exhibits 1 and 2, respectively.

Arikawa-Hirasawa I teaches that mice lacking the perlecan gene show severe cartilage disorganization of the columnar structures of chondrocytes and defective endochondral ossification. Further, Arikawa-Hirasawa I teaches that in the cartilage of perlecan-null nice, the cartilage matrix contained reduced and disorganized collagen fibrils and glycosaminoglycans,

suggesting that perlecan has an important role in matrix structure. *See*, Arikawa-Hirasawa I, Abstract. In addition, Arikawa-Hirasawa I teaches that chondrocyte proliferation is diminished and the prehypertrophic zone is reduced in perlecan-null nice. Arikawa-Hirasawa further notes that the skeletal abnormalities seen in the perlecan-null nice are similar to defects caused by activating mutations in FGFR3, and those of Fgfr3 gain-of-function mice.

That perlecan is important in cartilage formation is further borne out in studies in humans. Arikawa-Hirasawa II examined individuals with dyssegmental dysplasia, Silverman-Handmaker and isolated the genetic lesions underlying the disorder as mutations in the human perlecan gene. These mutations are predicted to cause a frame-shift of the translation of the mRNA, leading to a truncated perlecan protein. An analysis of the cartilage matrix from the patients showed that the cartilage stained poorly with antibodies to perlecan, and that the perlecan was not secreted but was degraded within the cell.

In view of the teachings of Arikawa-Hirasawa I and II, Applicants submit that, given that perlecan plays an essential and important role in cartilage formation and development both in mice and humans, and that WARP interacts with perlecan, one ordinarily skilled in the art would know how to make and use the polypeptide of the instant invention—shown to form in situ part of the ECM and interact with perlecan—as a marker for ECM integrity. Applicants submit that one ordinarily skilled in the art would extrapolate the results from perlecan to WARP and would expect that perturbations in WARP might lead to defects in ECM integrity. With the knowledge gained from studies of perlecan and the instant specification, one of ordinarily skill in the art would know to correlate WARP with ECM integrity. As such, Applicants submit that the claims are enabled.

In view of the amendments and remarks made above, Applicants respectfully request that the Examiner withdraw the enablement and written description rejections under 35 U.S.C. § 112, first paragraph.

The Rejections Under 35 U.S.C. § 102

The Claims Are Not Anticipated By WO2001/018022 or US20060003323

The Office Action contends that claims 1-2, 4, 7-8 and 11 are rejected under 35 U.S.C. § 102(b) as anticipated by International Patent Publication No. WO2001/018022 ("the

'022 publication") filed August 31, 2000. The Office Action further contends that claims 1-2, 4, 7-8 and 11 are rejected under 35 U.S.C. § 102(e) as anticipated by U.S. Patent Publication No. US2006/0003323 ("the '323 publication"), for the reasons made of record in the March 31, 2006 Office Action and as understood by Applicants in the October 2, 2006 Response.

Applicants have amended claim 4 to recite that the nucleotide sequence is capable of hybridizing to full-length SEQ ID NO:5 at specific stringency conditions. As currently amended, and for the reasons made of record in the October 2, 2006 Response, Applicants submit that the amended claims are not anticipated by the '022 publication or the '323 publication. Accordingly, Applicants respectfully request that the Examiner withdraw the rejections under 35 U.S.C. § 102.

Conclusion

Applicants respectfully request entry of the above amendments, consideration of the remarks made herein and those made in the October 2, 2006 Response, and allowance of the pending claims. Applicants submit that the present application is in condition for allowance at least for the reasons set forth herein. If the present application is not considered to be in condition for allowance by the Examiner, Applicants request an interview with the Examiner to discuss the present application and the prior art of record. Applicant's Attorney Walter M. Egbert may be reached at telephone number (212) 408-2500 to schedule a mutually convenient date and time and to provide assistance or additional information as required.

Applicants believe that no additional fee is due in connection with filing of this Supplemental Response. However, if any fee is required, or if any overpayment has been made, Applicants authorize, in the Transmittal Form and Fee Transmittal, the Director to charge any fees, or credit or any overpayments made, to Deposit Account 02-4377.

Respectfully submitted,

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